Overview of
Imazalil Risk Assessment

Introduction

This document summarizes EPA's human health, environmental fate and transport, and ecological risk findings for the pesticide imazalil, as presented fully in the documents, "Imazalil: HED Risk Assessment for the Reregistration Eligibility Decision (RED) Document," dated April 28, 2000, and "Environmental Risk Assessment for the Reregistration of Imazalil," dated September 22, 1999. The purpose of this overview is to help the reader understand the conclusions reached in the risk assessments by identifying the key features and findings of the assessments. References to relevant sections in the complete documents are provided to allow the reader to find the place in these assessments where a more detailed explanation is provided. This overview was developed in response to general comments from the public which indicated that EPA's risk assessments were difficult to understand, that they were too lengthy, and that it was not easy to compare the assessments for different chemicals due to the use of different formats.

These imazalil risk assessments and additional supporting documents, are posted on EPA's Internet website (http://www.epa.gov/pesticides/imazalil.htm) and are available in the Pesticide Docket for public viewing. Meetings with stakeholders (i.e., growers, extension officials, commodity group representatives and other government officials) will be held to discuss the risk assessments, the identified risks and solicit input on risk mitigation strategies, if needed. This feedback will be used to complete the Reregistration Eligibility Decision (RED) document, which will include the resulting risk management decisions. The Agency plans to conduct a close-out conference call with interested stakeholders to describe the regulatory decisions presented in the RED.

Risks summarized in this document are those that result only from the use of imazalil. The Food Quality Protection Act (FQPA) requires that the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." The reason for consideration of other substances is due to the possibility that low-level exposures to multiple chemical substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the other substances individually. The Agency did not perform a cumulative risk assessment as part of this reregistration review of imazalil because the Agency has not yet initiated a review to determine if there are any other chemical substances that have a mechanism of toxicity common with that of imazalil**.** If the Agency identifies other substances that share a common mechanism of toxicity with imazalil, then a cumulative risk assessment will be conducted that includes imazalil once the final framework the Agency will use for conducting cumulative risk assessments is available. Further, the Agency is in the process of developing criteria for characterizing and testing endocrine disrupting chemicals and plans to implement an Endocrine Disruptor Screening Program in 2002. Imazalil will be reevaluated at that time and additional testing may be required.

Use Profile

- **Fungicide (systemic)**: Registered for post-harvest treatment of citrus fruits, for seed treatment of barley and wheat prior to planting, and in egg handling facilities. There is also an import tolerance for bananas.

- **Formulations:** Formulated as impregnated material (14.9% active ingredient(ai)), liquid (up to 31% ai), emulsifiable concentrate (up to 68.25% ai), and flowable concentrate (10% ai).

- **Methods of Application:** Applied by seed treatment methods, drenches, smoke generators, fruit waxing equipment, and hand held equipment.

- **Use Rates:** For treating citrus, the maximum rate by wax treatment is 2,000 ppm (1.665 lb/100 gal). The seed treatment maximum application rate is 0.01008 lb ai/100 lb (slurry-type seed treatment). In egg handling facilities (hatchery and equipment), the maximum rates are 0.00032 lb/1,000 ft^3 for spray and 0.022 lb/1,000 ft^3 for smoke generator.

- **Annual Poundage:** Estimates for total annual domestic use averages approximately 6 thousand pounds of active ingredient. Crops with the highest percent crop treated are grapefruit, tangerines, lemons, and limes. In terms of pounds applied, oranges, grapefruit, and lemons account for the greatest agricultural use.

- **Pending Food Uses**: Previously submitted petitions to add certain new uses and to establish new tolerances for pears, melons, and sweet corn will be assessed during the development of the RED. Although the current dietary risk assessment does not specifically address these potential uses, the Agency intends to evaluate the impact of adding these uses on the dietary risk cup, prior to completing the RED.

- **Registrants:** Jansen Pharmaceutica (basic producer) and Makhteshim-Agan of North America

Human Health Risk Assessment

Acute Dietary Risk (Food)

(For a complete discussion, see section 4.2 of the Human Health Risk Assessment)

Acute dietary risk is calculated considering foods eaten in one day (consumption) and imazalil residue values in or on the food eaten by the general population and each population subgroup of interest. The consumption distribution can either be multiplied by a residue point estimate for a deterministic-type (i.e., Tier I/II) exposure assessment, or used with a residue distribution in a Tier III probabilistic-type (Monte Carlo) exposure assessment. A risk estimate that is less than 100% of the acute Population Adjusted Dose (aPAD) (the dose at which an individual could be exposed on any given day that would not be expected to result in adverse health effects) does not exceed the Agency's level of concern.

The Agency performed a probabilistic Tier 3 (Monte Carlo) acute dietary exposure assessment to estimate the dietary risks associated with the reregistration of imazalil. To estimate dietary exposure, the Agency used USDA Pesticide Data Program (PDP) monitoring data, field trial data, and calculated livestock anticipated residues (ARs). For all PDP analyses below the Limit of Detection (LOD), the Agency assigned a value equal to ½ LOD (weighted average of all laboratory limits of detection) where the crop was known to be treated with imazalil.

Acute risk estimates from exposures to food, associated with the use of imazalil do not exceed the Agency's level of concern. The estimated acute dietary risk (food only) is 15% of the aPAD at the 99.9^{th} percentile for the sub-population, females (13-50 years). (The Agency identified only one suitable endpoint and sub-population for assessing acute dietary risk.)

- The Dietary Exposure Evaluation Model (DEEM™) was used to estimate acute dietary exposures from consumption of foods that contain imazalil residues.

- The most significant contributors to exposure were grapefruit (~14%), oranges (~54%), and bananas (~28%), all of which had USDA/PDP monitoring data.

- The toxicological endpoint selected for the acute dietary assessment is based on an increased incidence of resorptions and decreased number of fetuses from a developmental toxicity study in rabbits (NOAEL= 5 mg/kg/day) where the LOAEL is 10 mg/kg/day.

- The Uncertainty Factor is 100X; 10X to account for interspecies extrapolation and 10x to account for intraspecies variability.

- The FQPA Safety Factor is 3X for acute assessments. It was reduced from 10X because there is no evidence of susceptibility in rat and rabbit developmental studies, but not removed entirely in light of qualitative evidence of susceptibility found in the 2-generation reproduction study in rats.

- The acute Population Adjusted Dose (aPAD) is 0.017 mg/kg/day (acute reference dose (RfD) 0.05 mg/kg/day ÷ 3X FQPA safety factor) and is only applicable to Females, 13-50 years old.

Chronic Dietary Risk (Food)

(For a complete discussion, see section 4.2 of the Human Health Risk Assessment)

Chronic dietary risk is calculated by using the average consumption value for food and average residue values on those foods over a 70-year lifetime. A risk estimate that is less than 100% of the chronic RfD (the dose at which an individual could be exposed over the course of a lifetime and no adverse health effects would be expected) does not exceed the Agency's level of concern. The cPAD is the chronic reference dose (cRfD) adjusted for the FQPA Safety Factor.

Chronic risk estimates from exposures to food do not exceed the Agency's level of concern. The chronic dietary (food only) risk estimate is <3% of the cPAD, for the U.S. Population and all subpopulations.

- The toxicity endpoint for the chronic dietary assessment is systemic toxicity, decreased body weight gain, increased liver weight, and increased liver enzyme activity based on the results of a one year chronic toxicity study in the dog (NOAEL = 2.5 mg/kg/day). These effects were observed at 20 mg/kg/day (LOAEL).

- The Uncertainty Factor is100X; 10X for inter-species variation and 10X for intra-species extrapolation.

- The 10x FQPA Safety Factor is 10X. EPA retained the factor for chronic exposure scenarios because of qualitative evidence of increased susceptibility following pre- and postnatal exposure to imazalil in a 2-generation reproduction study in rats and because of a data gap for a developmental neurotoxicity study.

- The major contributors to imazalil exposure were represented by USDA PDP monitoring data.

- The chronic Population Adjusted Dose (cPAD) is 0.0025 mg/kg/day (chronic RfD 0.025 mg/kg/day ÷ 10X FQPA safety factor).

Cancer Dietary Risk (Food)

(For a complete discussion, see section 4.2 of the Human Health Risk Assessment)

Like chronic dietary risk, cancer dietary risk is calculated by using the average consumption values for food and average residue values for those foods over a 70-year lifetime. The chronic exposure value is typically combined with a linear low-dose (Q1*) approach to

determine the lifetime (cancer) risk estimate. The Agency generally considers risks greater than 1×10^{-6} (i.e., greater than one in one million) to exceed its level of concern for cancer dietary exposure.

For imazalil, the Agency has not yet made a final determination whether the linear low-dose (Q_1^*) model or a threshold cancer model is most appropriate. The registrant is currently conducting studies to address which model is appropriate. In the interim, the Agency has utilized the standard Q_1^* model in the current risk assessment, but will reconsider that decision when results of the test data become available. The cancer dietary risk estimate for imazalil using the Q_1^* model is 2.1×10^{-6} $(mg/kg/day)^{-1}$, which slightly exceeds the Agency's target value.

- Imazalil is classified as "Likely to be carcinogenic in humans," according to EPA's July 1999 Draft Guidelines for Carcinogenic Assessment. Carcinogenicity studies in rodents indicate imazalil is carcinogenic to male Swiss albino mice and Wistar rats, based on a significant increase in liver adenomas and combined adenomas/carcinomas. In rats, there was also an increased incidence of combined thyroid follicular cell adenomas/carcinomas.

- Based on current science policy and absent information supporting a mode of action in test animals, EPA quantified the human cancer risk by a linear low-dose (Q_1^*) extrapolation. The most potent unit risk, $Q_1^*(mg/kg/day)^{-1}$ for imazalil based on male mouse liver adenoma and/or carcinoma combined tumor rates is 6.1×10^{-2} $(mg/kg/day)^{-1}$ in human equivalents.

- The three most significant contributors to the estimated cancer risks are bananas (11%), grapefruit (20%), and oranges (38%).

Drinking Water Dietary Risk

(For a complete discussion, see section 4.3 of the Human Health Risk Assessment)

Drinking water exposure to pesticides can occur through groundwater and surface water contamination. EPA considers both acute (one day) and chronic (lifetime) drinking water risks and uses either modeling or actual monitoring data, if available, to estimate those risks. To determine the maximum allowable contribution of treated water allowed in the diet, EPA first looks at how much of the overall allowable risk is contributed by food, then calculates a "drinking water level of comparison" (DWLOC) to determine whether modeled or monitoring levels exceed this level.

The Agency uses a DWLOC as a surrogate to capture risk associated with exposure from pesticides in drinking water. The DWLOCs represent the maximum contribution to the human diet (in ppb or μg/L) that may be attributed to residues of a pesticide in drinking water after

dietary exposure is subtracted from the aPAD or cPAD. Risks from drinking water are assessed by comparing the DWLOCs to the estimated environmental concentrations (EECs) in surface water and groundwater. Drinking water modeling is considered to be an unrefined assessment and provides high-end estimates.

In this case, the Agency concludes that no population group is exposed to imazalil residues in drinking water at a level that poses an acute or chronic risk of concern. EEC levels for all populations do not exceed acute or chronic DWLOC levels. Cancer DWLOCs were not calculated since the dietary cancer risk estimate already slightly exceeds the Agency's level of concern of 1×10^{-6}, suggesting that any drinking water exposure derived from a model combined with dietary food consumption would further exceed the Agency's level of concern. However, the Agency has qualitatively concluded that humans will not be exposed to imazalil in drinking water because imazalil is unlikely to contaminate surface or ground waters.

- Estimated drinking water concentrations for ground water are based on the SCI-GROW model, which is a Tier I assessment that provides a high-end estimate.

- Estimated drinking water concentrations for surface water are based on the GENEEC model, which is a Tier I assessment that also provides a high-end estimate.

- For acute risk, potential exposure to imazalil from drinking water derived from surface water does not exceed the Agency's level of concern. Neither the surface water acute EEC of 0.072 ppb nor the groundwater estimate of "negligible" exceeds the DWLOC of 500 for females 13-50 years.

- For chronic risk, the EECs for surface water (GENEEC, 0.013 ppb) and groundwater (SCI-GROW, 0 ppb) were less than the chronic DWLOC (87 ppb for general population and 25 ppb for children 1-6 years), indicating that chronic exposure to imazalil in food and water is not of concern.

Residential Risk

There are no residential uses of imazalil currently registered nor any uses of imazalil in or around the home, around public buildings or recreational areas where children might be exposed.

Aggregate Risk

(For a complete discussion, see section 5.0 of the Human Health Risk Assessment)

The aggregate risk assessment for imazalil examines the combined risk from exposure through food and drinking water only because there are no residential uses for imazalil. Generally, combined risks from these exposures that are less than 100% of the aPAD and cPAD are not considered to be a risk concern. Exposures to imazalil from dietary (food and water) sources are not of concern, as discussed above. Although water exposure does not represent a significant source of exposure to imazalil, residues in food alone slightly exceed the Agency's level of concern for cancer risk.

Occupational Risk

(For a complete discussion, see section 4.4 of the Human Health Risk Assessment)

People can be exposed to a pesticide while working through mixing, loading, or applying a pesticide, and reentering a treated site. Handler and worker risks are measured by a Margin of Exposure (MOE) which determine how close the occupational exposure comes to a No Observed Adverse Effect Level (NOAEL) taken from animal studies. Generally, MOEs greater than 100 do not exceed the Agency's level of concern. For workers entering a treated site, Restricted Entry Intervals (REIs) are calculated to determine the minimum length of time required before workers or others are allowed to re-enter.

In the case of imazalil, dermal and inhalation risks for handlers are assessed separately since the end effects for the toxicological endpoints for these exposures are not the same and Agency policy is to not aggregate the risks (inhalation plus dermal) if the toxicological effects are not similar. Handler exposures to imazalil are expected to be short-, intermediate- and long-term by dermal and/or inhalation routes of exposure. Life-time cancer risk is also calculated for the various handler scenarios.

Occupational Handler Summary

EPA identified 13 handler exposure scenarios resulting from mixing/loading and applying (liquid and dry) imazalil for seed treatment (on-farm and commercial seed-treatment equipment); for citrus, mixing/loading and applying various formulations by drenching, waxing and foaming equipment; and in chicken hatcheries, mixing/loading and applying liquid formulation for high pressure handwand applications and applying/lighting smoke canisters.

- For the short-term dermal toxicity endpoint, the NOAEL of 160 mg/kg/day is based on skin effects and swollen livers from a 21-day dermal study in the rabbit. The LOAEL is 250 mg/kg/day.

- For estimating intermediate- and long-term dermal risks, EPA uses oral animal studies in the absence of appropriate dermal toxicity studies. The dermal absorption factor is 40%, based upon the maximum blood concentration observed in a rat dermal absorption study. This factor was used for converting dermal exposures to equivalent oral doses. (A comparison of oral and dermal toxicity studies suggests that the actual dermal absorption rate for imazalil may be lower; the apparent rate may be as low as 4% in the rabbit. Thus, the dermal absorption factor may over predict the amount of imazalil available to elicit a toxic response, making both the intermediate- and long-term dermal risks assessments conservative.)

- For the intermediate-term dermal toxicity endpoint, the NOAEL of 16 mg/kg/day is based on severe liver effects at the oral LOAEL of 32 mg/kg/day from a 90-day feeding study in the rat.

- For the long term dermal toxicity endpoint, a NOAEL of 2.5 mg/kg/day is based on systemic toxicity, decreased body weight gain, increased liver weight and increased liver enzyme activity at the oral LOAEL of 20 mg/kg/day from the one year feeding study in the dog

- For estimating short-, intermediate- and long-term inhalation risks, EPA uses oral animal studies in the absence of appropriate inhalation toxicity studies. EPA assumes 100% of the inhaled imazalil dose is absorbed by the body.

- For the short-term inhalation toxicity endpoint, a NOAEL of 5 mg/kg/day is based on increased incidence of resorptions and decreased number of fetuses from a developmental toxicity study in rabbits (NOAEL= 5 mg/kg/day) where the LOAEL is 10 mg/kg/day.

- For the intermediate-term and long-term inhalation toxicity endpoints, a NOAEL of 2.5 mg/kg/day is based on the above one year feeding study in the dog.

- As described above, based on current science policy and absent information supporting a mode of action in test animals, EPA quantified the human cancer risk by a linear low-dose (Q_1^*) extrapolation. The most potent unit risk, $Q_1^*(mg/kg/day)^{-1}$ for imazalil based on male mouse liver adenoma and/or carcinoma combined tumor rates, is 6.1×10^{-2} $(mg/kg/day)^{-1}$ in human equivalents.

- No chemical-specific exposure studies are available for the occupational assessment. Surrogate-based exposure assessments for each scenario are used from the Pesticide Handler Exposure Database (PHED) and other available data.

Certain exposure scenarios lack surrogate data to assess risk. Data are needed to assess the following occupational handler scenarios:

- Mixer/loader - Supporting drenching of citrus
- Applicator - Drenching, foaming, and waxing citrus
- Applicator - Lighting and using smoke canister for chicken hatchery

Handler Risk Scenarios

The results of the non-cancer short-, intermediate- and long-term dermal and inhalation risk assessments show that all scenarios provide MOEs greater than or equal to 100 at baseline attire (i.e., long pants, long sleeved shirts, no gloves), except for mixing/loading liquid formulation for waxing equipment. With the addition of PPE, the MOE for this scenario is also much greater than 100. In this case, PPE are long pants, long sleeved shirt and gloves.

There are a few handler scenarios with cancer risks of concern; however, of the 13 scenarios evaluated, none are worse than 1×10^{-4} when PPE is employed. Most scenarios are

no worse than 1 x 10^{-7}. Most imazalil labels currently prescribe the following PPE for all handlers: long sleeved shirt and long pants, chemical-resistant gloves, shoes, socks, and protective eyewear.

The following assumptions and factors were used for completing the handler cancer risk assessment:

- The average body weight of 70 kg is used, representing a typical adult.
- Exposure duration is assumed to be 35 years. This represents a typical working lifetime.
- Lifetime is assumed to be 70 years.
- Exposure frequencies used in the calculations are, 250 days for chicken hatcheries, 60 days for on-farm and commercial seed treatment,10 days for private citrus applicator and on farm seed treatment, and 100 days for commercial citrus applicator.

Post-Application Occupational Risk

EPA has determined that there is potential worker exposure to persons handling citrus fruits after waxing or foaming, to persons working in egg handling facilities, and to persons handling treated seeds.

- For citrus, the main activities are sorting/culling/ or packing of products following wax treatment. The Agency has no data specifically addressing the exposure from those activities. Exposure estimates for citrus in the risk assessment were derived from residue chemistry data, surface area calculations, and a reentry study for citrus found in the scientific literature.

- For post harvest dermal (hand) exposure from waxed citrus, an adequate MOE (120) exists for intermediate term effects under the baseline exposure scenario (long pants, long sleeved shirt, no gloves).

- Using a Q_1* analysis, the estimated lifetime cancer risk for post treatment citrus workers was estimated to be 6.68 x 10^{-4} under the baseline exposure scenario.

- Citrus exposure estimates are considered very conservative because (1) although imazalil is usually part of a wax matrix which substantially impedes transfer to the skin, it was assumed that all of the imazalil on the treated surface could be transferred to the skin; and (2) the transfer coefficients for the hands were obtained from a field study in which contact with contaminated foliage was highly probable; a conveyor belt treatment line would be unlikely to have such a high degree of contact.

- Given the nature of the activities at egg handling facilities, EPA believes that there is minimal risk involved in dermal or inhalation exposure to imazalil in chicken hatcheries; therefore no post-application inhalation or dermal risk assessment was performed for reentry following smoke generator or spraying applications in chicken factories.

- For seed treatment, the Agency has determined that soil-incorporated, post-application agricultural exposure is negligible as long as the soil where the seed is sown is not directly contacted.

Ecological Risk

To estimate potential ecological risk, EPA integrates the results of exposure and ecotoxicity studies using the quotient method. Risk quotients (RQs) are calculated by dividing exposure estimates by ecotoxicity values, both acute and chronic, for various wildlife species. RQs are then compared to levels of concern (LOCs). Generally, the higher the RQ, the greater the potential risk. Risk characterization provides further information on the likelihood of adverse effect occurring by considering the fate of the chemical in the environment, communities and species potentially at risk, their spatial and temporal distributions and the nature of the effects observed in studies.

Environmental Fate and Transport

- Imazalil is moderately water soluble, very stable to hydrolysis, photodegrades relatively rapidly, degrades very slowly in soil under aerobic conditions, is immobile in soils, is not expected to volatilize, and has a high octanol water partition coefficient.

- Based on the above environmental fate properties, and with consideration of the product formulation, the application methods, and the application rates, EPA believes that the immobile and relatively persistent parent compound is unlikely to be found in the the environment.

Terrestrial Organism Risk

- Based on the available data (Appendix 3), Imazalil is practically nontoxic to slightly toxic to birds, and moderately toxic to rats following the acute exposure. A chronic toxicity study with mallard ducks indicated effects on embryo viability and hatchability, while body weight loss was observed with bobwhite quails. In the two generation rat chronic study, effects on body weight and litter size were observed.

- On the basis of risk quotients, imazalil use at the proposed application rates will not result in an acute risk to either avian or mammal species. No LOCs were exceeded due to the low application rate and minimal exposure.

Aquatic Organism Risk

- Imazalil is moderately toxic to both freshwater fish and invertebrates in terms of acute toxicity (LC_{50} range of 1.48 - 3.99 ppm for fish and EC_{50} of 3.54 ppm for daphnids)

- On the basis of risk quotients, imazalil will not result in accedences of highly acute, acute risk use, or acute endangered species of concern for freshwater organisms. No acute levels of concern for freshwater organisms were exceeded due to the extremely low exposure, which is attributable to the low application rate (0.01 lb ai/A) and the seed treatment end-use (only 1% residue left on soil surface)

- Because of the extremely low exposure and relatively low acute toxicity to freshwater organisms, acute toxicity testing for estuarine aquatic organisms and all chronic testing have been waived.

Incident Data

- There are no fish or wildlife incident reports regarding imazalil in EPA's Ecological Incident Information System.

Summary of Pending Data

The Agency expects to receive additional studies on imazalil in June, 2002. The registrant is trying to demonstrate the mode of (cancer) action for Imazalil is either unique to laboratory animals or such that the pesticide should be regulated as a threshold carcinogen. The registrant voluntarily elected to conduct the following study:

- Determination of Acute and Sub-acute Hepatocyte Cell Proliferation in Mice.

In addition, the following confirmatory data requirements have been initially identified by the Agency:

Toxicology Data for OPPTS Guidelines:

- 870.6300 Developmental Neurotoxicity in Rats
- 870.6200 Acute Neurotoxicity Study in Rats
- 870.6200 Subchronic Neurotoxicity Study in rats

Product and Residue Chemistry Data for OPPTS Guidelines:

- 860.1340 Residue analytical Method - Animal Commodities
- 860.1360 Multiresidue Method
- 860.1480 Egg and poultry fumigation Study

Occupational Exposure Data for OPPTS Guidelines

- Exposure study of citrus treatment applicators (wax application and foamers)
- Post application inhalation and dermal exposure following smoke generator or spraying applications in chicken hatcheries